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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/544,045	04/06/2000	Brian Lee Sauer	OMRF 178	8128

23579 7590 07/29/2003

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EXAMINER
SANDALS, WILLIAM O

ART UNIT	PAPER NUMBER
1636	25

DATE MAILED: 07/29/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action	Application No. 09/544,045	Applicant(s) SAUER ET AL.	
	Examiner William Sandals	Art Unit 1636	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 7-9-2003 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE. Therefore, further action by the applicant is required to avoid abandonment of this application. A proper reply to a final rejection under 37 CFR 1.113 may only be either: (1) a timely filed amendment which places the application in condition for allowance; (2) a timely filed Notice of Appeal (with appeal fee); or (3) a timely filed Request for Continued Examination (RCE) in compliance with 37 CFR 1.114.

PERIOD FOR REPLY [check either a) or b)]

a) ☒ The period for reply expires *3* months from the mailing date of the final rejection.

b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection. ONLY CHECK THIS BOX WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

1. ☒ A Notice of Appeal was filed on *09 July 2003*. Appellant's Brief must be filed within the period set forth in 37 CFR 1.192(a), or any extension thereof (37 CFR 1.191(d)), to avoid dismissal of the appeal.

2. ☐ The proposed amendment(s) will not be entered because:

   (a) ☐ they raise new issues that would require further consideration and/or search (see NOTE below);

   (b) ☐ they raise the issue of new matter (see Note below);

   (c) ☐ they are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or

   (d) ☐ they present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____.

3. ☐ Applicant's reply has overcome the following rejection(s): 102(b) over Ackroyd; 102(b) over Miller.

4. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).

5. ☒ The a)☐ affidavit, b)☐ exhibit, or c)☒ request for reconsideration has been considered but does NOT place the application in condition for allowance because: *see attached*.

6. ☐ The affidavit or exhibit will NOT be considered because it is not directed SOLELY to issues which were newly raised by the Examiner in the final rejection.

7. ☐ For purposes of Appeal, the proposed amendment(s) a)☐ will not be entered or b)☐ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

   The status of the claim(s) is (or will be) as follows:

   Claim(s) allowed: _____.

   Claim(s) objected to: _____.

   Claim(s) rejected: *1-49*.

   Claim(s) withdrawn from consideration: _____.

8. ☐ The proposed drawing correction filed on _____ is a)☐ approved or b)☐ disapproved by the Examiner.

9. ☐ Note the attached Information Disclosure Statement(s)(PTO-1449) Paper No(s). _____.

10. ☐ Other: _____

William Sandals

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APPLICATION NO./ CONTROL NO.	FILING DATE	FIRST NAMED INVENTOR / PATENT IN REEXAMINATION	ATTORNEY DOCKET NO.
09/544045	4/6/00	Sauer et al.	

EXAMINER	
William Sandals	
ART UNIT	PAPER
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Commissioner for Patents

Arguments presented in Paper No. 23, filed July 9, 2003 at page 14 assert that the instant claims are not drawn to gene therapy, but rather to methods of identifying variant recombinases.

Claims 1-23 are drawn to a method of identifying variant recombinases. Dependent claims 24-49 are drawn to a method of producing a site specific recombination, and claims 43, 44 and 46 are specifically drawn to the practice of the invention in a multicellular organism, which may be a mammal. Independent claims must embrace all of the limitations of the dependent claims, thereby making all of claims 1-47 readable on the practice of the invention in a multicellular organism or animal, which constitutes gene therapy.

Arguments presented in Paper No. 23, page 14 assert that the modification of the germ line of an animal would ensure the enablement of the claimed invention.

This argument is not commensurate in scope with the limitations of the claims, and as such does not address the grounds of rejection.

The arguments presented in Paper No. 23, page 14 further asssert that the placement of a LoxP reporter DNA at the ROSA26 locus in a mouse gives reliable and reproducible expression of a reporter gene whose expression changes upon site-specific DNA recombination. It is asserted that genomic modifications such as this example may be used to express a recombinase gene in a transgenic animal.

These limitations are not present in the claims. As such they are not commensurate with the scope of the claims.

The argument continues in Paper No. 23, page 14 asserting that it is not necessary to change the phenotype of an animal, but it is only necessary to change the phenotype of a single cell in an animal to practice the instant invention.

Somatic manipulations are discussed in the final rejection. The final rejection makes it clear that attempts to effect transfection of genes in vivo are not well understood, and are not predictable.

Insofar as this argument applies to germ line genomic modifications, as stated in the final rejection, "response to arguments" section, the teachings of Sigmund (of record) state that the expression of a gene in a transgenic animal is unpredictable, as demonstrated by the lack of predictability of expression in animals with different genetic backgrounds. This point is made to emphasize the lack of understanding of transgene expression in transgenic animals.

Arguments presented in Paper No. 23, page 15 assert that making an insertion of a transgene into the germline of an animal will avoid the pitfalls of somatic cell delivery problems.

The limitation of introducing a transgene into the germline of an animal is not commensurate in scope with the limitations of the claimed invention. As stated above, this approach does not eliminate the uncertainties of genetic therapy.

Arguments presented in Paper No. 23, page 18 regarding Miller et al. assert that Miller et al. do not present data for recombination between a wild type recombination site and a variant recombination site where both the first and second recombination sites are variant recombination sites.

Miller et al. teach at page 725, column 2 "Action of Int-h3 with an attachment site mutation", that it is known that the first and second site may be variants in the same construct. Therefore, Miller et al. make obvious the use of a construct with variant

recombination sites which correspond to [redacted]nstant claimed first and second variant recom[redacted]ion sites in a method of identifying a variant recombinase.

Arguments presented in Paper No. 23, page 18 assert that Miller et al. do not teach bringing a mutant Int recombinase together with a pair of mutant Att sites.

Miller et al. teach at page 725, column 2 "Action of Int-h3 with an attachment site mutation", that "[a] 100 fold reduction in recombination is seen if one or both Att sites of lambda AttL-AttR carry the Att mutation". This is a clear statement that both Att24 recombination sites may be used in an assay for recombinase activity. Therefore, Miller et al. do make obvious the use fo a construct with two recombinable, variant recombination sites in combination with a variant racombinase.

William Sandals

July 22, 2003

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